REMARKS

Status of the Claims

Claims 25-29 and 34 are pending and claim 34 is under consideration in this application, claims 1-24 and 30-33 having been cancelled without prejudice to their being pursued in a separate application and claims 25-29 having been withdrawn for allegedly being drawn to separate inventions. Claim 34 stands rejected. After entry of the amendments made in this application, claims 25-29 and 35-44 will be pending and claims 35-44 will be under consideration in this application, claim 34 having been cancelled without prejudice to it being presented in a separate application and new claims 35- 44 having been added.

New claims 35-44 are supported throughout the specification. For the convenience of the Examiner, these claims are recited below with examples of textual support in the specification for various claim terms indicated in parentheses after the terms.

35. A method of stimulating regenerative growth of damaged neuronal axons (e.g., page 8, line 14, to page 9, line 3; page 28, line 8, to page 29, line 16) in a patient with traumatic nervous system damage (e.g., page 14, lines 7-8; page 19, lines 7-8), the method comprising delivering directly at a traumatic lesion site (e.g., page 14, lines 7-8; page 19, lines 7-8) in a nerve in a patient, in an amount effective to suppress inhibition of neuronal axon growth (e.g., page 11, line 1; page 29, line 22; claim 21 as originally filed), a Rho family antagonist selected from the group consisting of:

(a) a C3 ADP-ribosyl transferase (e.g., page 10, line 4; page 11, line 23); and

(b) biologically active fragments of (a) (e.g., page 5, lines 5-7; page 10, lines 21-22; claim 9 as originally filed),

wherein the antagonist stimulates regenerative growth of damaged neuronal axons across (e.g., page 8, line 25) and through (e.g., page 29, lines 4-16) the lesion site, and

wherein the antagonist has the ability, when scrape loaded into PC12 cells *in vitro* (e.g., page 23, lines 14-21; page 25, lines 18-19; page 27, lines 19-21), to produce outgrowth of PC12 cell neurites, the PC12 cells being plated on a growth inhibitory substrate selected from the group consisting of myelin and myelin-associated glycoprotein substrate (e.g., page 6, line 22, to page 7, line 13).

36. The method of claim 35, wherein the nerve is a nerve in the central nervous system (e.g., Field of the Invention section on page 1; claims 5, 6, and 9 as originally filed).

37. The method of claim 35, wherein the nerve is an optic nerve (e.g., page 8, line 14, to page 9, line 3; page 28, lines 10-12).

38. The method of claim 35, wherein the lesion site comprises a site of nerve crush injury (e.g., page 28, line 15, to page 29, line 16).

39. The method of claim 35, wherein the regenerative growth comprises a twisted path of growth through the lesion site (e.g., page 29, line 7).

40. The method of claim 35, wherein the regenerative axon growth extends 250 micrometers (μm) or more past the lesion site (e.g., page 29, lines 11-16).

41. The method of claim 35, wherein the regenerative axon growth is up to 1 millimeter (mm) past the lesion site (e.g., page 29, lines 13-14; page 32, lines 3-4).

42. The method of claim 35, wherein the nervous system damage is selected from the group consisting of a spinal cord injury, a spinal cord lesion, and a surgical nerve lesion (e.g., page 14, lines 7-8; page 19, lines 7-8).

43. The method of claim 35, wherein the antagonist is administered with a pharmaceutical carrier or delivery system (e.g., page 14, line 3; page 18, line 19).

44. The method of claim 38, wherein the delivery is from gelfoam wrapped around the damaged nerve at the crush site (page 28, lines 15-17).

Applicants point out that the term "biologically active fragments [of C3 ADP-ribosyltransferase]" as recited in line 6 of claim 35 does not refer to an unlimited range of compounds. The full-length C3 ADP-ribosyltransferase ("C3") protein is relatively small (23 kDa; see page 11, line 24 of the specification) and the fragments must be "biologically active" (see, e.g., definition on page 5, lines 6-7, of the specification) and have the *in vitro* activity specified by the second "wherein" clause of newly added claim 35. Thus, one of skill in the art, given the teaching of the specification (e.g., Example 1), and the well-developed state of the art, would at the priority date of the instant application have been readily able to identify fragments falling within the scope of claim 35 using entirely routine experimentation.

Priority

From the comments on page 2, line 18, to page 3, line 8, of the Office Action, Applicants understand the Examiner's position to be that the instant application should not have the priority of the Canadian Patent Application No. 2,214,841 (the '841 application; filed October 31, 1997) because treatment of PC12 cells *in vitro* is not an art-accepted model for predicting *in vivo* neuronal growth. Applicants strongly disagree with this position.

In support of her position of data obtained from PC12 cells *in vitro* not being an art-accepted model for predicting *in vivo* neuronal growth, the Examiner refers to Crutcher et al. Applicants point out that Crutcher et al. was published more than ten years before the filing date of the '841 application. In the interim, significant progress in the understanding of neuronal damage and repair was made and it was demonstrated that PC12 cells responded *in vitro* to growth inhibitory substances in a manner very similar to primary neurons *in vivo*. Relevantly in

this regard, Crutcher et al. states: "Many in vitro methods have only recently been established" (line 8 of the Introduction section on page 297).

The Information Disclosure Statement (IDS) filed herewith includes references published after the publication of Crutcher et al. but before, or shortly after, the filing date of the '841 application, which show that the previously widely known inability of damaged neuronal axons to grow *in vivo* was also seen in PC12 cells cultured *in vitro* under appropriate conditions [see, for example: Tomaselli et al. (1990) Neuron, 5:651-662; Rubin et al. (1995) Eur. J. Neuroscience, 7:2524-2529; Daniels (1998) EMBO J., 17(3):754-764]. Should the Examiner so wish, additional references indicating the correlation between *in vitro* behavior of PC12 cells and *in vivo* failure of neuronal repair will be provided.

In addition, Applicants draw the Examiner's attention to the fact that such a correlation is actually referred to in the '841 application, e.g., in the Background section it is stated that "[c]onsistent with observations *in vivo*, it was found that dominant negative Rac expressed in PC12 cells disrupts neurite outgrowth in response to NGF" (page 3, lines 11-13). Relevantly, Applicants have also included a requirement in new independent claim 35 that the antagonist used in the claimed *in vivo* method have the activity on PC12 cells *in vitro* taught by the '841 application.

In light of the above considerations, Applicants respectfully submit that the PC12 cell culture model was an art-accepted *in vitro* model of *in vivo* axonal growth inhibition at the filing date of the '841 application and thus request that instant claims be accorded, as a priority date, the filing date of the '841 application (i.e., October 31, 1997).

35 U.S.C. § 102 (e) rejections

(a) Claim 34 stands rejected as allegedly being anticipated by Liao et al., U.S. Patent No. 6,180,597 (the '597 patent).

Claim 34 is cancelled.

In addition, for the reasons given above, the priority date of the instant claims (new claims 35-44) is **October 31, 1997**. The earliest priority date of the '597 patent is **March 19,**

1998. Thus, Applicants respectfully submit that the '597 patent is not prior art with respect to the instant claims. For this reason the rejection is moot.

Applicants respectfully submit that, even if the '597 patent were prior art with respect to the instant application, neither canceled claim 34 nor newly added claims 35-44 would be anticipated by it.

(b) Claim 34 stands rejected as allegedly being anticipated by Johnson et al., U.S. Patent No. 5,851,786 (the '786 patent).

Claim 34 has been cancelled and thus the rejection is moot.

Applicants respectfully submit that the '786 patent does not anticipate new claims 35-44.

From the comments on page 6, line 17, to page 8, line 15, of the Office Action, Applicants understand the Examiners position to be that, in disclosing the administration of Botulinum C3 exoenzyme to an animal subject, the '786 patent inherently anticipated claim 34. Applicants respectfully disagree with this position for the following reasons.

The '786 patent teaches methods for identifying compounds capable of regulating actin polymerization, stress fiber formation and/or focal adhesion assembly as well as methods to treat or control certain diseases with such compounds (see, e.g., Abstract; claim 40; column 1, lines 37-48; column 2, lines 15-19 and 35-36; column 3, lines 30-38; column 17, lines 22-58; column 18, line 8-42). However, new claims 35-44 of the current application are distinguished from the teachings of the '786 patent in that these new claims are directed to a method of stimulating regenerative growth of damaged neuronal axons in a patient with traumatic nervous system damage. The '786 patent is silent with respect to stimulation of regenerative growth of traumatically damaged neuronal axons and thus does not anticipate application of a compound such as C3 in the treatment of patients with traumatic nervous system damage.

The object of the treatment methods disclosed by the '786 patent is to "regulate cellular function" (column 2, line 24) and the methods are, in particular, "useful for preventing or treating diseases involving abnormal growth or the migration of cells from one location in an animal to another." (column 17, lines 23-25). It is thus clear that the treatment methods of the

'786 patent are directed at inhibiting unwanted cellular activity (e.g., cell growth) in a variety of diseases. On the other hand, the present claims are directed at enhancing a cellular activity (i.e., neuronal axon growth) in order to repair traumatic damage to nerves. While the '786 patent does refer to treating two nervous system diseases (Parkinson's and Alzheimer's diseases; column 17, line 34), it is clear (from the above cited text) that the inventors contemplated doing so by inhibiting undesirable cellular responses in these diseases rather than by enhancing neuronal axon growth as the present claims require in order to repair traumatic neuronal injury. Thus, not only does the '786 patent not disclose methods or repairing traumatic damage to nerves, it does not even suggest them.

In that the '786 patent neither explicitly nor implicitly discloses each and every element of claim 35, the '786 patent does not anticipate claim 35 or any of the claims dependent on claim 35 (i.e., claims 36-44).

CONCLUSION

In summary, for the reasons set forth above, Applicants maintain that the pending claims patentably define the invention. Applicants request that the Examiner reconsider the rejections as set forth in the Office Action, and permit the pending claims to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number listed below.

Enclosed is a request for an automatic extension of time and a check in payment of the extension in time. Please charge any other fees or make any credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 12552-002001.

Respectfully submitted,

Date: 6/2/04

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